

Acute-on-chronic liver failure

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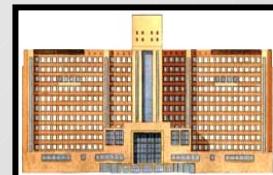
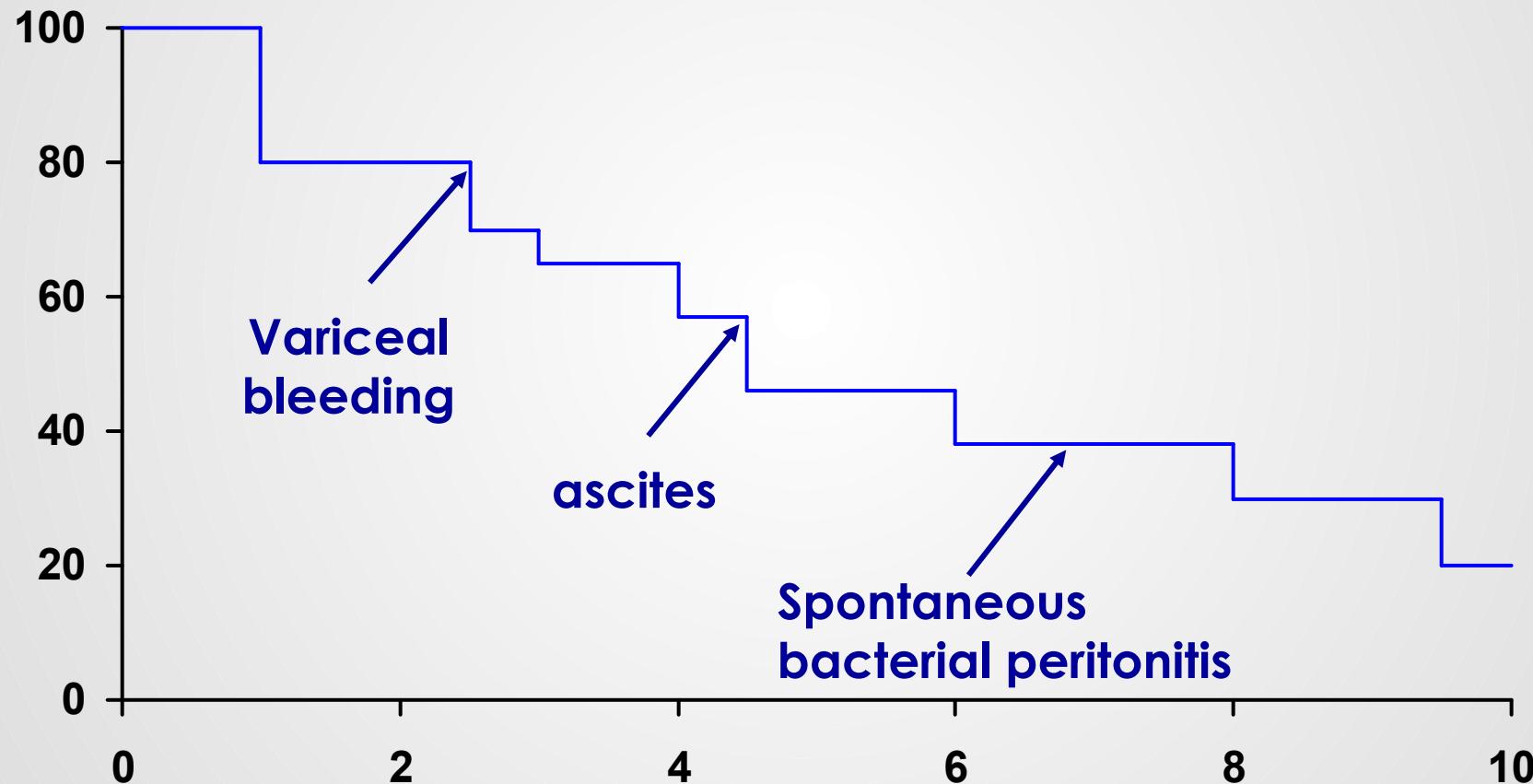
PARIS, Palais des Congrès

Organised by: **Pr Patrick MARCELLIN**
Association for the Promotion of Hepatologic Care
(APHC)



Grants from Gilead, Astellas

Natural history of cirrhosis



Variceal bleeding

Improvement in the outcome

Author	Period	Patients	In-hospital mortality
El-Serag HB	1981-82	1339	29.6%
	1988-91	3636	20.8%*
Lo GH	2005-07	93	4%

El-Seragh HB et al. Am J Gastroenterology 2000; 95:3566

Lo GH et al. GUT 2009; 58: 1275

*p < 0,05

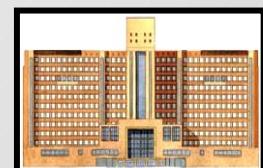


Spontaneous bacterial peritonitis

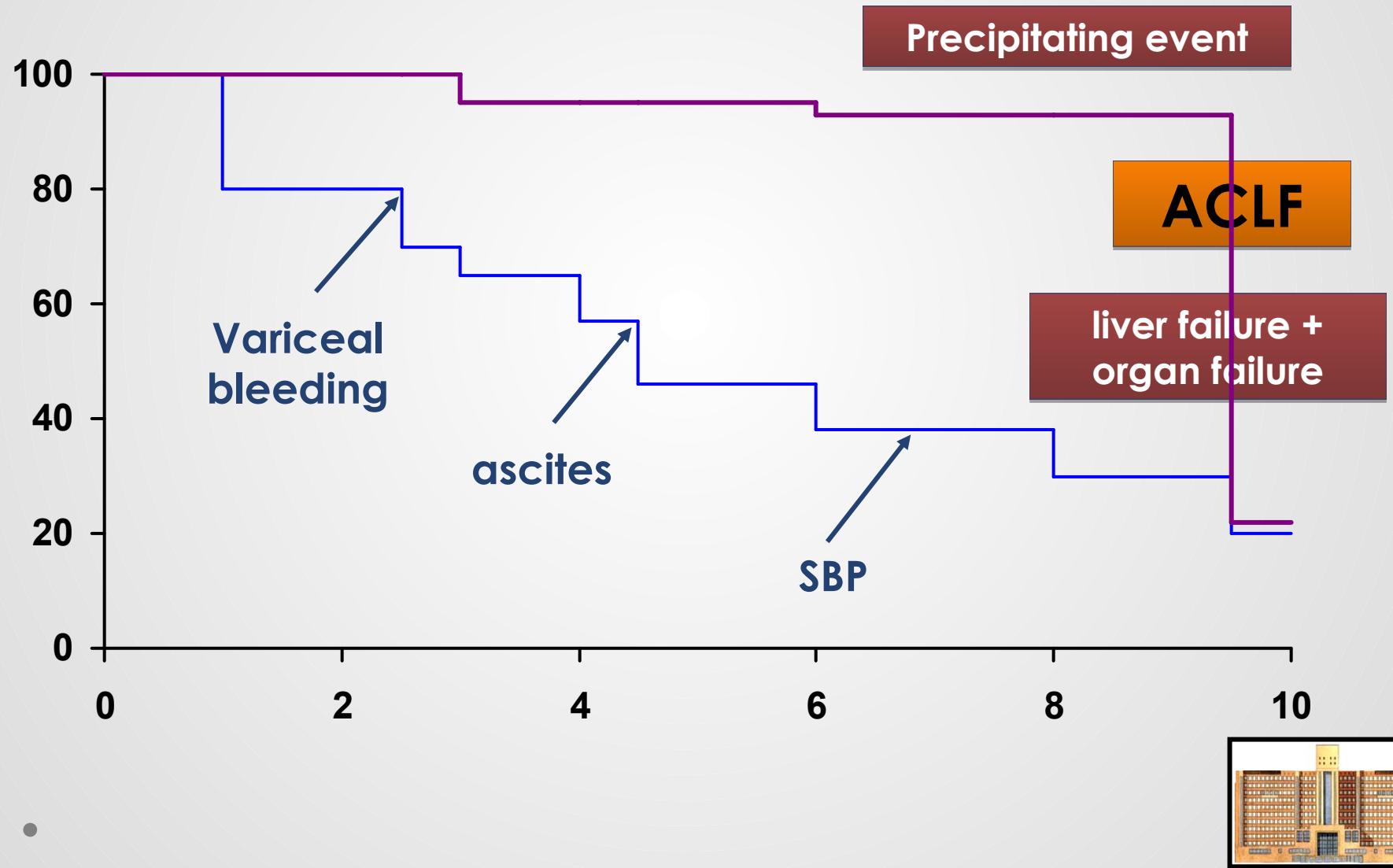
Improvement in the outcome

Author	Year	Patients	In-hospital mortality
Ariza J	1986	14	62%
Ariza J	1991	44	50%
Sort P	1999	63	29%
	-	63	10%*

* Antibiotics+ albumin



Natural history: changes



ACLF: need for a definition

- **ACLF is not:**

- ✓ Acute / subacute liver failure
 - Non cirrhotic underlying liver
- ✓ Decompensation of cirrhosis
 - Ascites
 - Variceal bleeding
 - SBP
 - Encephalopathy
- ✓ Alcoholic hepatitis

- **What is ACLF:**

- ✓ Underlying cirrhosis
- ✓ Occurrence of organ / system failure
- ✓ High mortality rate
 - 28-day mortality > 15%

1343 patients with cirrhosis
29 centers
415 ACLF
928 no ACLF



Defining ACLF

- **ACLF grade 1**
 - ✓ Single kidney failure
 - ✓ Single failure of the liver (bilirubin), coagulation, circulation, respiration and creatinine from 1.5 to 1.9 mg/dL
 - ✓ Single cerebral failure and creatinine from 1.5 to 1.9 mg/dL
- **ACLF grade 2**
 - ✓ Two organ failures
- **ACLF grade 3**
 - ✓ 3 or more organ failures
- Moreau R et al. Gastroenterology 2013; 144: 1426

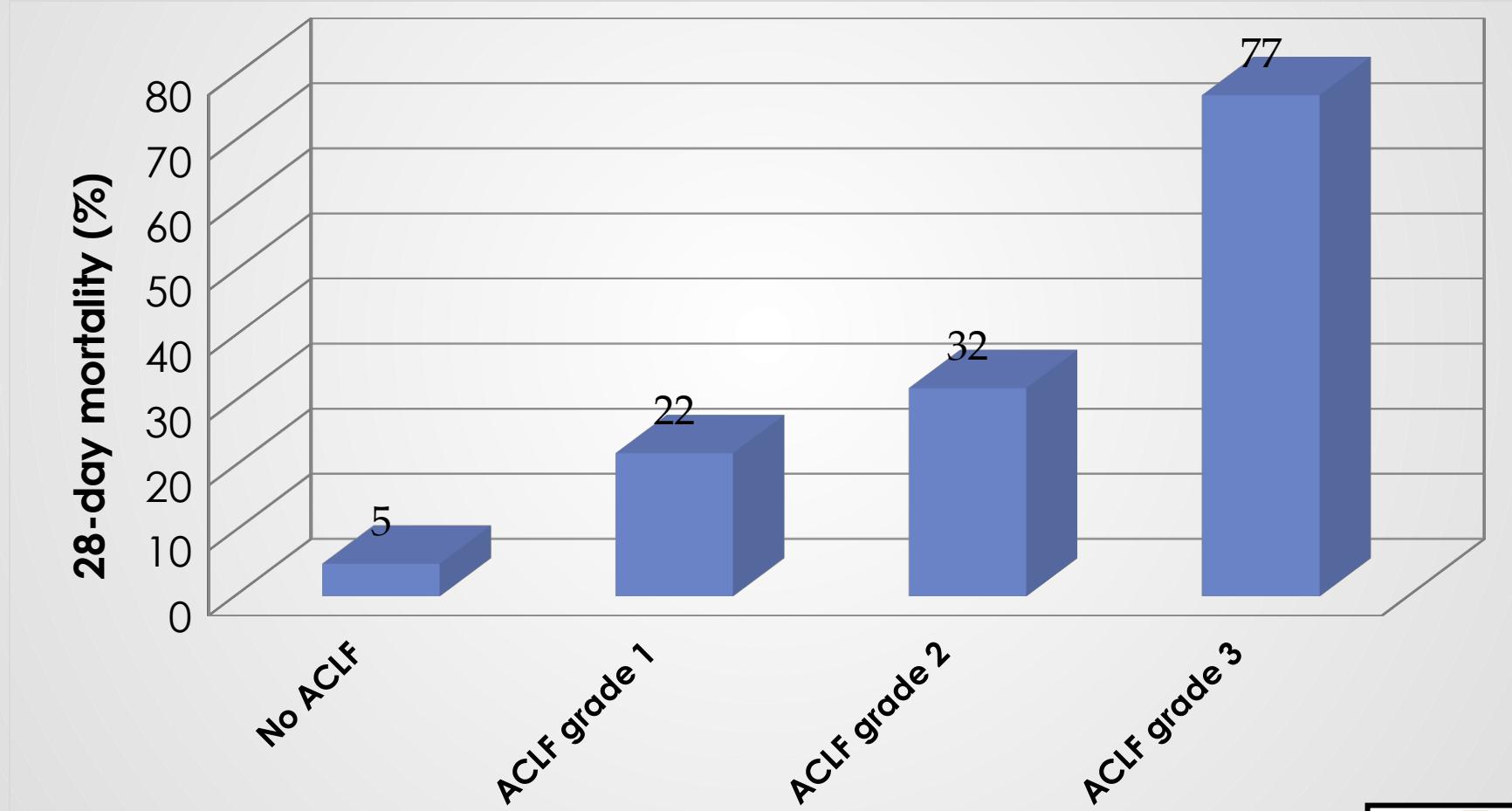


Defining organ failure

- Liver failure: bilirubin $\geq 200 \mu\text{mol/L}$
- Kidney failure: creatinine $\geq 180 \mu\text{mol/L}$
- Coagulation failure: INR ≥ 2.5 and/or platelets $\leq 20*10^9/\text{L}$
- Circulatory failure: use of vasopressors
- Cerebral failure: grade III or IV encephalopathy
- Respiratory failure: $\text{PaO}_2/\text{FiO}_2 \leq 200$
-



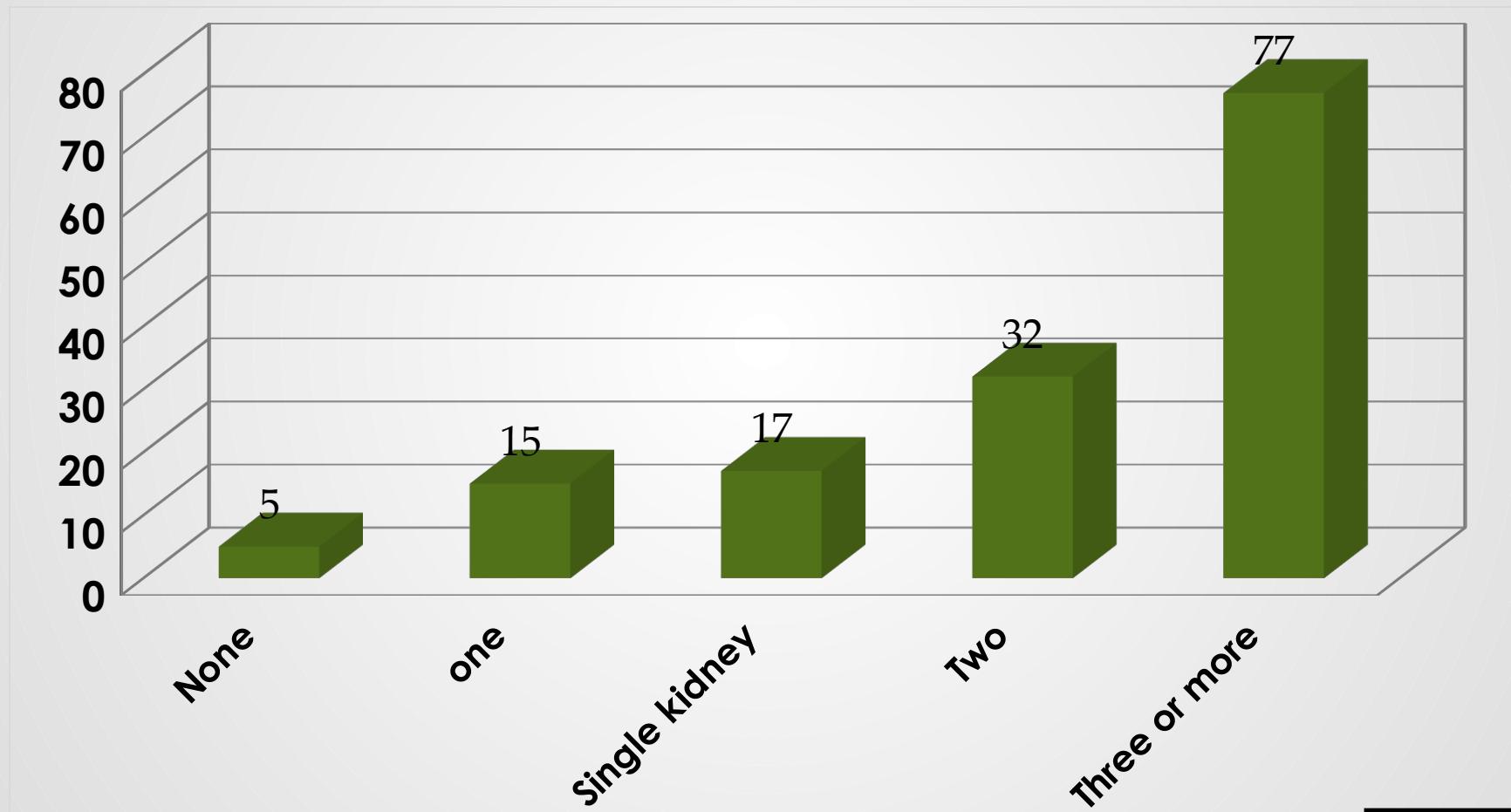
Mortality according to ACLF grade



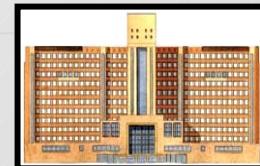
- Moreau R et al. Gastroenterology 2013; 144: 1426



Mortality according to organ failure



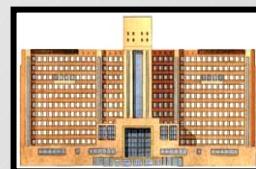
- Moreau R et al. Gastroenterology 2013; 144: 1426



Characteristics of patients with ACLF

	No ACLF	ACLF	p
Age	58	56	0.02
Cause of cirrhosis			
Alcohol	49%	60%	<0.01
HCV	21%	13%	<0.01
Ascites	63%	78%	<0.001
Bacterial infection	22%	32%	<0.001
No previous decompensation	28%	23%	ns
No precipitating event	59%	43%	<0.001

- Moreau R et al. Gastroenterology 2013; 144: 1426



Characteristics of patients with ACLF

	No ACLF	ACLF	p
Bilirubin ($\mu\text{mol/L}$)	81	319	<0.001
Creatinine ($\mu\text{mol/L}$)	88	202	<0.001
INR	1.5	2.3	<0.001
Na (mmol/L)	135	133	<0.001
Platelets ($*10^9/\text{L}$)	110	100	0.02
Leukocytes ($*10^9/\text{L}$)	6.6	9.7	<0.001
CRP (mg/L)	25	40	<0.001

- Moreau R et al. Gastroenterology 2013; 144: 1426



Predictive factors of ACLF and prognosis

Development of post enrolment ACLF		
	OR	p
CLIF-SOFA score	1.39	<0.001
Leukocyte count	1.06	0.01
Ascites at admission	1.67	0.03
28-day mortality in patients with ACLF		
CLIF-SOFA score	1.34	<0.001
Leukocyte count	1.08	<0.01

- Moreau R et al. Gastroenterology 2013; 144: 1426



Mechanisms involved in ACLF

- **Precipitating events**

- ✓ **Bacterial infection**

- Initiation of systemic and portal circulatory dysfunction
 - Initiation of organ failure

- ✓ **HAV / HEV infection**

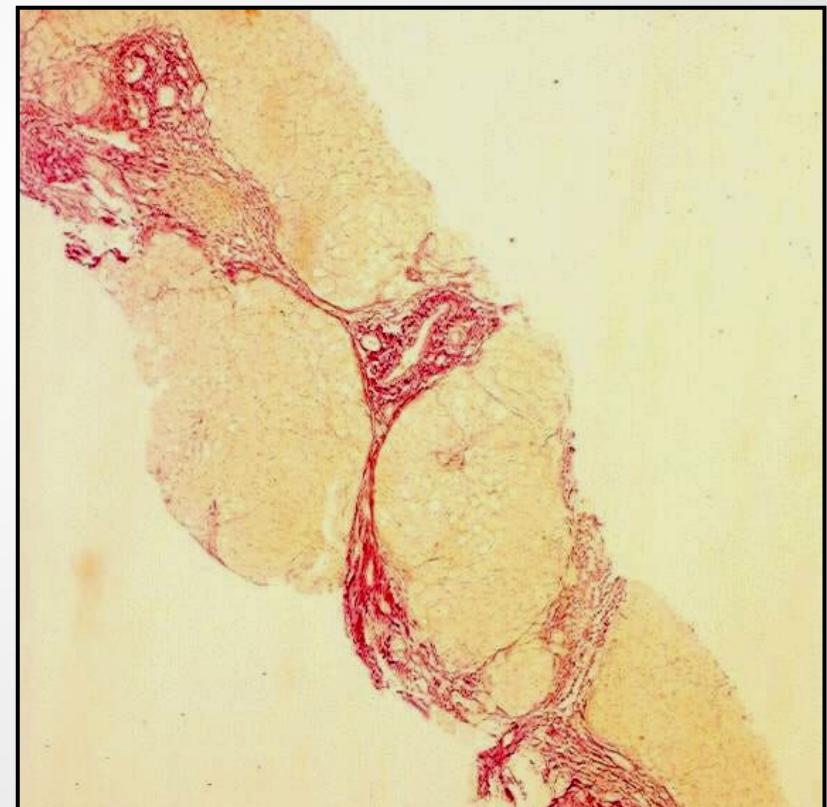
- Liver cell necrosis
 - Limited potential for regeneration

- ✓ **Drug induced**

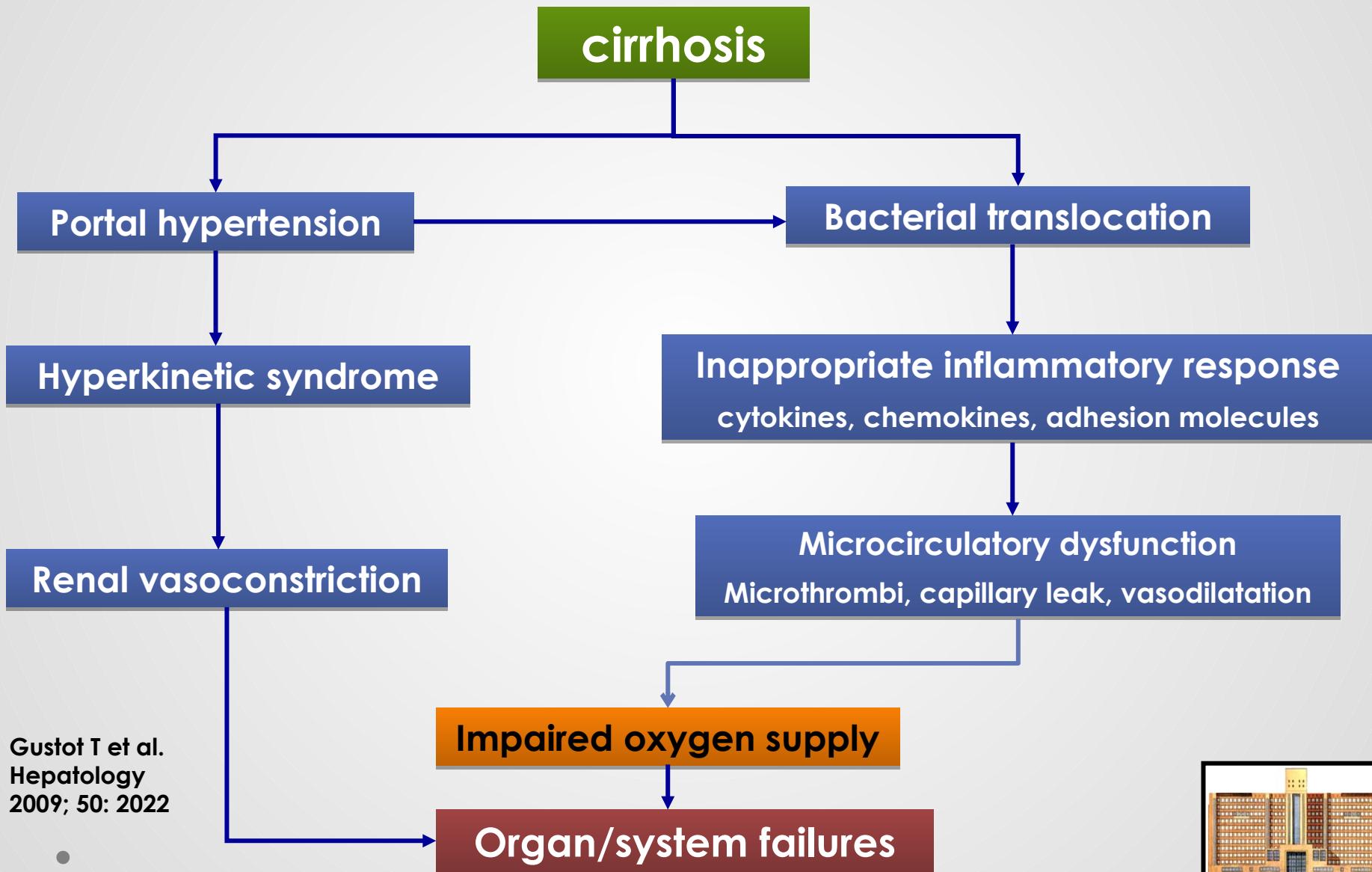
- Paracetamol
 - NSAIDs

- ✓ **Surgery**

- Bacterial infection
 - Encephalopathy
 - Ascites



Mechanisms involved in ACLF



Management of ACLF

- **Circulatory failure**

- ✓ Vasopressors

- **Renal failure**

- ✓ Terlipressin
 - ✓ Renal replacement therapy

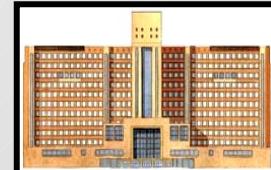
- **Cerebral failure**

- ✓ Rifaximin
 - ✓ Albumin dialysis

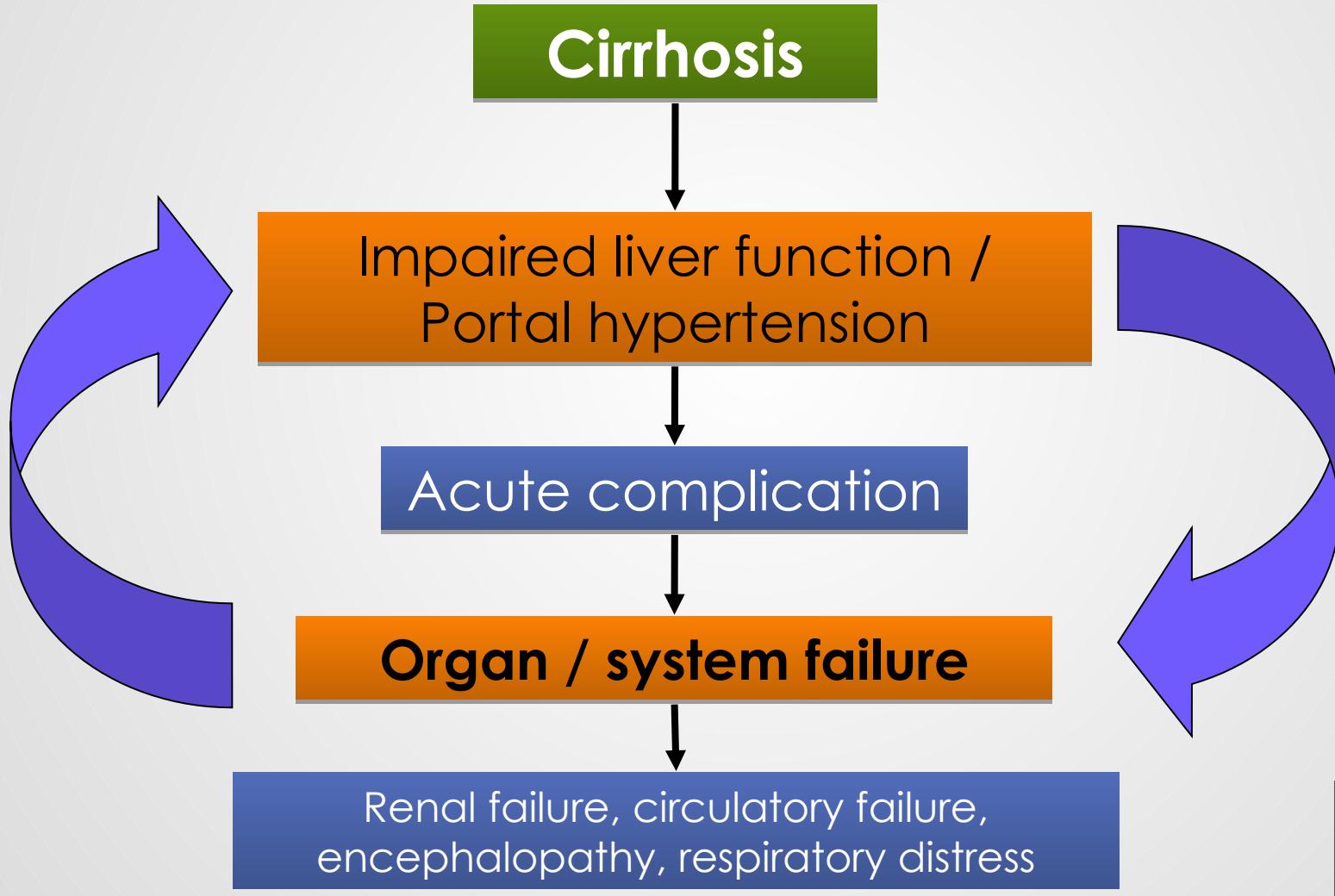
- **Respiratory failure**

- ✓ Oxygen
 - ✓ Mechanical ventilation

“Rescue” transplantation



The vicious circle of ACLF



How to exit: MARS ?

Randomized controlled trial in ACLF

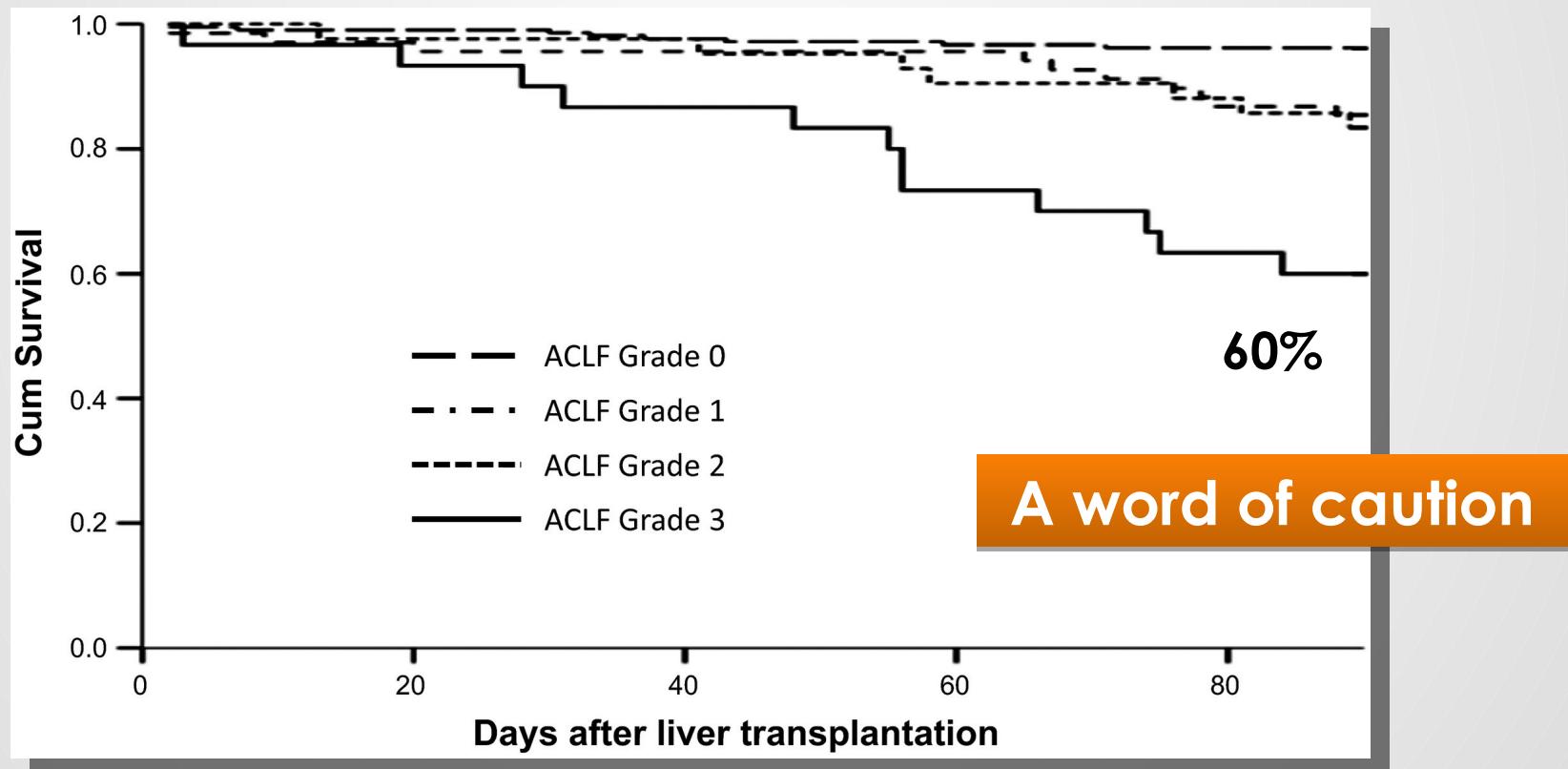
	MARS	Control	p
Patients	90	89	
MELD	26	24	ns
Hepatorenal syndrome	53%	53%	ns
Decrease in bilirubin	-26%	-9%	<0.001
Decrease in creatinine	-20%	-6%	ns
Decrease in platelets	-29%	-2%	<0.001
28-day survival (ITT)	61%	60%	ns

Banares R et al. Hepatology 2013; 57: 1153.



How to exit: transplantation?

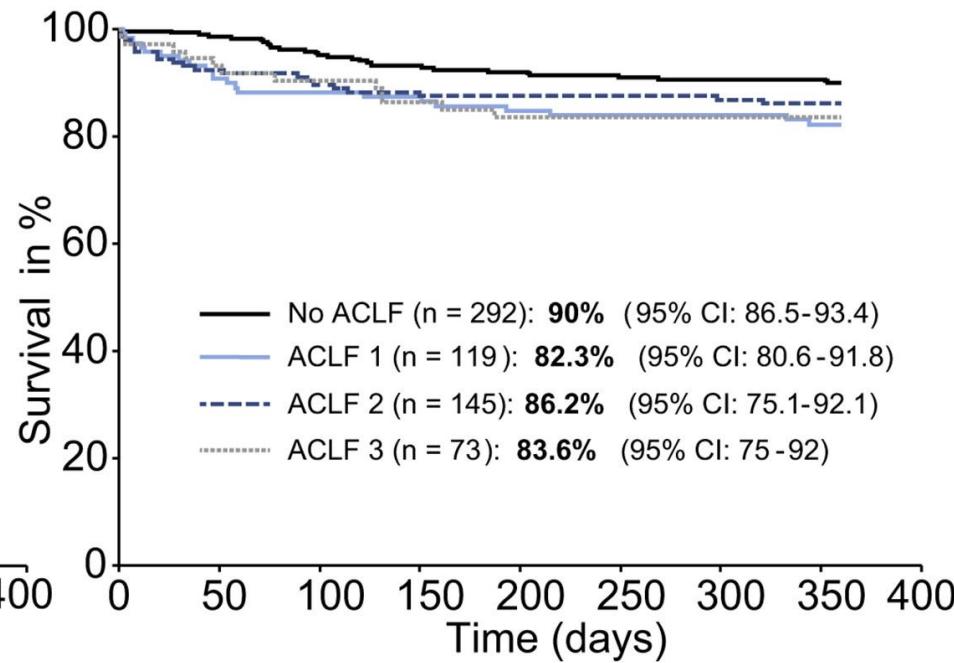
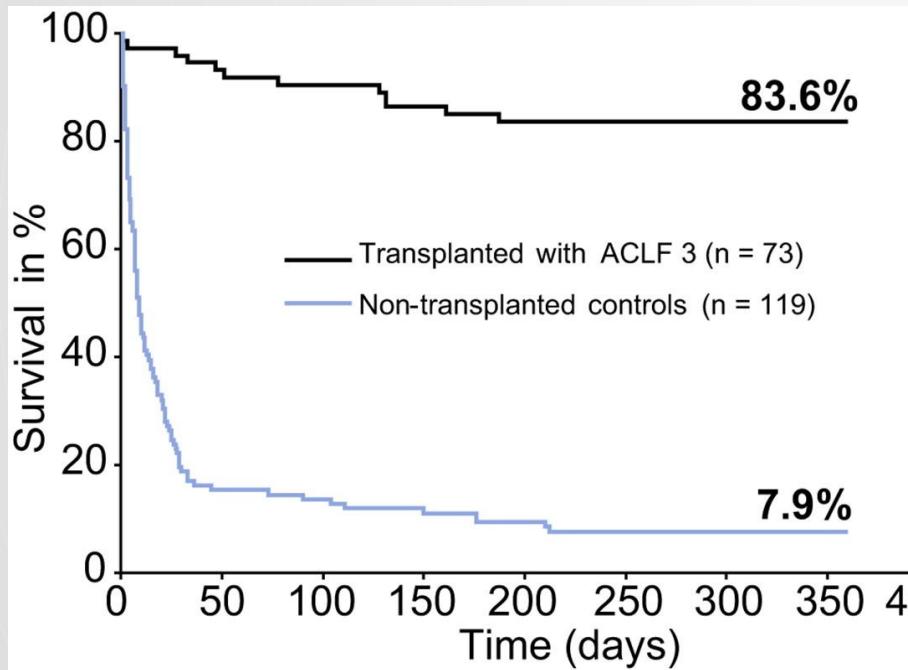
140 patients transplanted for ACLF
Single center study



- Levesque E et al. Liver Int 2017; 37:684.

How to exit: transplantation?

Multicenter study in France
73 patients wit ACLF 3

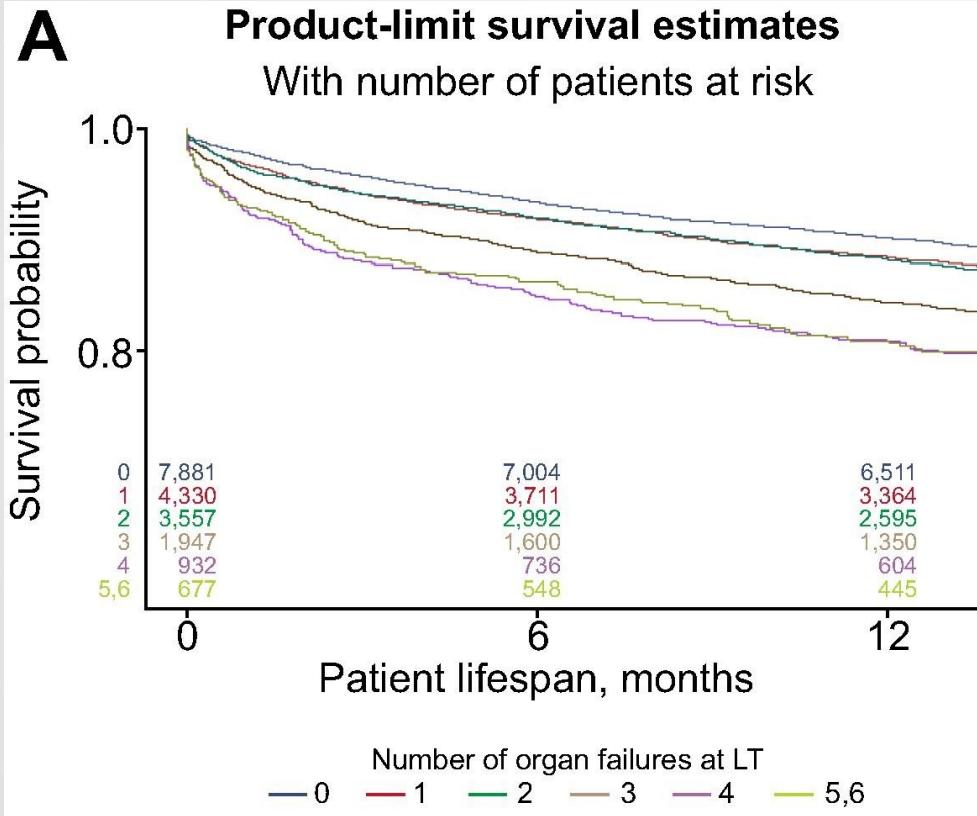


A more optimistic message



How to exit: transplantation?

UNOS registry-based study in the US



Problems with definitions
Multiple biases

An unrealistic message

- Thuluvath PJ et al. Journal of Hepatology 2018; 69: 1047.



Conclusions

- **ACLF : cirrhosis + organ failure + poor prognosis**
 - ✓ Definition clarified by the EASL-CLIF consortium
 - ✓ Definition of liver failure (bilirubin) still questionable
- **No previous decompensation in 23%**
- **No precipitating factor in 43%**
- **High leukocyte associated with increased mortality**
 - ✓ Role of exacerbated immune response (SIRS)
- **Each organ failure can be managed separately**
 - ✓ Vicious circle explaining high mortality
- **Transplantation: an option in the MELD era**
 - ✓ Limits to be defined to avoid futility
- **Prevention of ACLF in patients with cirrhosis**
 - ✓ Several studies in progress

